

**PREOPERATIVE USE OF INTRANASAL KETOROLAC TROMETHAMINE
(SPRIX[®]) IN PERIODONTAL FLAP SURGERY**

by

Stephen B. Hutton, DMD, MPH
Lieutenant, Dental Corps
United States Navy

A thesis submitted to the Faculty of the
Periodontics Graduate Program
Naval Postgraduate Dental School
Uniformed Services University of the Health Sciences
in partial fulfillment of the requirements for the degree of
Master of Science
in Oral Biology

June 2015

Naval Postgraduate Dental School
Uniformed Services University of the Health Sciences
Bethesda, Maryland

CERTIFICATE OF APPROVAL

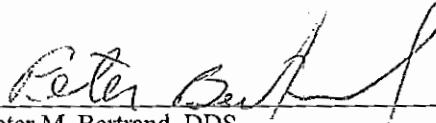
MASTER'S THESIS

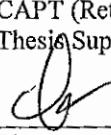
This is to certify that the Master's thesis of

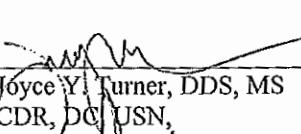
Stephen B. Hutton

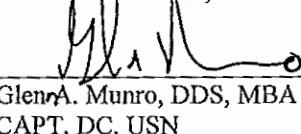
has been approved by the Examining Committee for the thesis requirement
for the Master of Science degree in Oral Biology at the June 2015 graduation.

Thesis Committee:


Peter M. Bertrand, DDS
CAPT (Ret), DC, USN
Thesis Supervisor


Thu P. Getka, DDS, MS
CAPT, DC, USN
Chairman, Periodontics Department

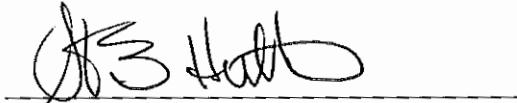

Joyce Y. Turner, DDS, MS
CDR, DC, USN
Associate Professor, Periodontics Department


Glen A. Munro, DDS, MBA
CAPT, DC, USN
Dean, Naval Postgraduate Dental School

The author hereby certifies that the use of any copyrighted material in the thesis manuscript titled:

Preoperative Use Of Intranasal Ketorolac Tromethamine (Sprix®) In Periodontal Flap Surgery

is appropriately acknowledged and, beyond brief excerpts, is with the permission of the copyright owner.



Stephen B. Hutton
Periodontics Graduate Program
Naval Postgraduate Dental School
June 2015

NAVAL POSTGRADUATE DENTAL SCHOOL
STEPHEN B. HUTTON

2015

This thesis may not be re-printed without the expressed written permission of the author.

ABSTRACT

PREOPERATIVE USE OF INTRANASAL KETOROLAC TROMETHAMINE (SPRIX®) IN PERIODONTAL FLAP SURGERY

STEPHEN B. HUTTON, DMD, MPH
PERIODONTICS DEPARTMENT, 2015

Thesis directed by: Peter M. Bertrand, DDS
CAPT (Ret), DC, USN
Naval Postgraduate Dental School

Introduction: To reduce pain, analgesics intervene at sites of tissue damage, where pain-inducing cytokines are activated. Cytokines stimulate the cyclooxygenase (COX) pain pathway, causing pain and inflammation. Non-steroidal anti-inflammatory drugs (NSAIDs) induce analgesic action by preventing COX2 from being expressed. A 1989 Journal of the American Dental Association review recommended preoperative oral ibuprofen administration prior to procedures. However, a 2014 American Academy of Periodontology consensus report on periodontal regeneration indicated future research should focus on pain management strategies. Other NSAIDs, such as ketorolac tromethamine, are delivered rapidly and efficaciously to the bloodstream and may promote more effective analgesia for highly painful periodontal procedures.

Objective: Determine effect of a single 31.5 mg dose of intranasal ketorolac (INKT) compared to placebo given to patients 20 minutes prior to undergoing periodontal flap surgery on postoperative analgesic consumption and postoperative pain levels during the initial five postoperative days.

Methods: A comprehensive literature review using PubMed-MEDLINE identified appropriate studies related to analgesic control before, during, and after periodontal surgery. A double-blinded randomized parallel-arm controlled clinical trial was designed.

Results: Several options to perform preoperative analgesic management exist. Well-controlled, experimental evidence demonstrates post-operative pain levels and rescue drug consumption are reduced in patients managed with pre-operative NSAIDs. Yet, few studies have evaluated the use of INKT as an adjunct to pain control in the dental setting. Following design of the clinical trial in concert with Roxro pharmaceuticals, Roxro was acquired and the new parent company discontinued active promotion of SPRIX® (INKT) and sponsorship of clinical trials. The study was discontinued.

Conclusions: Preoperative analgesic administration may minimize pain and postoperative analgesic consumption. However, dental research has yet to evaluate in highly painful procedures, such as quadrant periodontal flap surgery, the effect of preoperative administration of INKT on postoperative dental pain levels and post-operative analgesic consumption.

TABLE OF CONTENTS

	Page
LIST OF TABLES	vi
LIST OF FIGURES	vii
LIST OF ABBREVIATIONS	viii
 CHAPTER	
I. INTRODUCTION	1
II. REVIEW OF THE LITERATURE	2
Nociception	2
Pain in Surgery	3
Analgesics in Surgery	5
Strategies to Reduce Postoperative Pain	10
Periodontal Surgery	10
Ketorolac Tromethamine to Manage Pain	13
Intranasal Ketorolac	14
Off-Label Use of Intranasal Ketorolac	20
Adolescent use of Intranasal Ketorolac	22
Modified SPRIX® for Migraine	22
Recent Advancements using Ketorolac	22
Summary	23
III. MATERIALS AND METHODS	25
IV. RESULTS	34
V. DISCUSSION	40
VI. CONLUSIONS	52
APPENDIX A Pain Diary Example	53
REFERENCES	54

LIST OF TABLES

Table		Page
1.	Table 1: Selected studies that evaluated postoperative outcomes following preoperative administration of NSAIDs	35

LIST OF FIGURES

Figure	Page
1. Figure 1: Effect of preoperative medication	34
2. Figure 2: Effect of preoperative medication	34
3. Figure 3: Type of Procedures Evaluating Pain After Preoperative Medication Administration	36
4. Figure 4: Types of analgesics used preoperatively	36
5. Figure 5: Type of medication used preoperatively	36
6. Figure 6: Method of Administration of Ketorolac When Administered Preoperatively	37

LIST OF ABBREVIATIONS

AERD	Aspirin Exacerbated Respiratory Disease
CNS	Central Nervous System
COX	Cyclooxygenase (Physiologic Enzyme)
CTG	Subepithelial Connective Tissue Autograft
FDA	Food and Drug Administration
FEV ₁	Forced Expiratory Volume in 1 Second
FGG	Free Gingival Autograft
GI	Gastrointestinal
GTR	Guided Tissue Regeneration
HCG	Human Chorionic Gonadotropin
IL	Interleukin (Cytokine Protein)
IM	Intramuscular
IN	Intranasal
IN _e	5% solution of ketorolac tromethamine containing 0.3% sodium glycolate "enhancer"
IV	Intravenous
IW	Intrawound
KT	Ketorolac Tromethamine
mg	Miligram
ml	Mililiter
ng	Nanogram
NMDA	N-methyl-D-aspartate (Glutamate Receptor Protein)
NPDS	Naval Postgraduate Dental School
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
PACU	Post Anesthesia Care Unit
PGE2	Prostaglandin E2 (Physiologic Lipid Compound)
PID	Pain Intensity Difference
PNIF	Peak Nasal Inspiratory Flow
PO	<i>per os</i> (Oral Administration)
PRN	pro re nata (As the Circumstance Arises)
ROX-828	SPRIX® Containing 6% Lidocaine
SPID	Summed Pain Intensity Difference
SPRIX®	Ketorolac Tromethamine Nasal Spray
t _{1/2}	Apparent half life of medication
Tc-DTPA	Tc-diethylenetriaminepenta acetic acid (Synthetic Macromolecule)
TXB2	Thromboxane B2 (Physiologic Lipid Compound)
VAS	Visual Analog Scale
VRS	Verbal Rating Scale
WRNMMC	Walter Reed National Military Medical Center

CHAPTER I: INTRODUCTION

Tissue insult may produce an inflammatory response, which can be associated with acute pain perception. Some surgical procedures tend to generate more postoperative pain than others, and increased scientific understanding of the physiologic inflammatory process has facilitated the development of analgesic medications to manage acute pain following surgery. Periodontal surgery requires acute postoperative pain management, and procedures such as subepithelial connective tissue autograft (CTG) transplant, free gingival autograft (FGG) transplant, guided tissue regeneration (GTR) and osseous resective surgery may provoke more pain on average than most other dental surgery procedures. Varying modalities of acute pain management for periodontal surgery exist in terms of quantity, type and duration of analgesic administration. Practitioners generally elect to use a non-opioid medication such as non-steroidal anti-inflammatory drugs (NSAID) or an opioid medication such as hydrocodone for the acute phase of the healing process. These two approaches have advantages and disadvantages in managing postoperative pain. This study will assess the effectiveness of preoperative administration of intranasal (IN) ketorolac tromethamine KT in periodontal flap surgery in terms of postoperative pain control and opioid consumption compared to placebo.

CHAPTER II: REVIEW OF THE LITERATURE

Nociception

Nociception is the stimulation of specific nerve receptors resulting in cognitive perception of pain as a result of electrochemical signals between the peripheral nerves and the brain, where neurologic impulses are received and interpreted. Nociception can be prevented through the use of anesthesia. Complete anesthesia is associated with four hallmark physiologic effects: analgesia, amnesia, akinesia and autonomic blockade. Injecting local anesthetic chemical compounds into the tissues adjacent nerve fibers to inhibit generation and conduction of electrical impulses along nerves to the brain, there is a loss of sensation in a localized area of the body. Tissue insult during surgery results in the generation of endogenous compounds of the body that will stimulate nerve receptors and cause nociception. Chemical compounds of local anesthetics are used to inhibit nociception during surgical procedures, but they are limited in their duration of action. After the effects of local anesthetics diminish, postoperative management of pain requires the use of analgesic medications to block the generation of the same endogenous nociceptive compounds by the body and/or block the conduction of nociceptive signals to the brain.

Ideal postoperative pain management harnesses the advantages of NSAID medications and opioids while minimizing their disadvantages. Administration of analgesic medications (opioid and/or non-opioid) preoperatively may improve the level of pain experienced postoperatively and reduce disadvantages by reducing total analgesic consumption following surgery.

Pharmaceutical development of NSAIDs is ongoing. Ketorolac tromethamine (KT) is a NSAID that is well documented for its successful postoperative pain management. It is now available for intranasal administration (SPRIX®). Some studies have evaluated the use of preoperative intranasal ketorolac on postoperative pain levels and rescue analgesic consumption following various surgical procedures. However, there has yet to be a randomized, controlled, experimental study of these variables in the context of periodontal flap surgery.

Pain in Surgery

For centuries, the study of pain has worked to understand etiology, characteristics, progression and effective treatment modalities. Turk and Okifuji define pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage” (Turk & Okifuji, 2010). Pain may be defined as acute or chronic based on time since the onset. However, the nature of pain should be represented both as a function of time and presence of pathology. Perception of pain that is short in duration and/or high in pathology suggests an acute process (Turk & Okifuji, 2010). Acute pain is interpreted by the brain from signals generated by high threshold free nerve endings known as nociceptive receptors that are stimulated by tissue insult. These signals are transmitted from peripheral tissues to second order neurons that reach the thalamus in the brain. Upper brain circuitry connected with the thalamus is where nociception is interpreted as pain.

Hyperalgesia is an increased pain response to a normally painful stimulus and allodynia is pain that is elicited by a stimulus is generally not considered painful (Turk & Okifuji, 2010). Hyperalgesia or allodynia are associated with changes nervous system

changes due to increased nociceptive intensity or duration of action. These changes are called sensitization and occur as nerve thresholds for transmitting potentially painful signals are lowered. Lowered thresholds can occur at the peripheral free nerve endings and centrally at neuronal synapses throughout the spinal cord and brain.

Chronic pain also is a function of sensitization and may be perpetuated by factors that are remote from the original etiology, such as stress, repetitive behaviors and comorbidities. For example, chronic back pain due to mechanical changes, irritable bowel syndrome and fibromyalgia are common comorbidities that are intensified by stress increases (Turk & Okifuji, 2010). The emotional experience of acute pain subsides when the underlying pathology causing the activation of nociceptive receptors is eliminated. However, when the increased excitability of neurons in the central nervous system (CNS) that defines central sensitization is established, tissues may appear normal while pain and emotional suffering persists. Woolf (2004) describes pain as either adaptive or maladaptive. Adaptive pain is an innate response to injury; the body manifests a heightened sense of awareness to injury in order to protect the site and allow for healing. Conversely, maladaptive pain presents as a chronic disease resulting from overwhelming pain stimulation to the nervous system.

Pain associated with surgery is an acute phenomenon. As nociceptive signals are transmitted from the surgical site, the CNS elaborates descending signals (endogenous anti-nociception) to reduce pain and protect the site of insult. These protective mechanisms include inhibition of nociceptive transmission and reparative inflammatory mechanisms that initiate healing and repair after insult. The tissue damage from surgery that fires the nociceptive system and yields pain is inflammatory in nature. A

hypersensitive pain response (sensitization) can result from tissue damage if pain is not adequately controlled. Difficulties with postoperative pain control may be related to addressing underlying conditions that affect the nociceptive threshold of the patient or the physiologic healing process. Successful treatment of the surgical patient includes effective acute pain management of peripheral sensitization due to inflammatory effects associated with tissue trauma. Resolution of the inflammatory response observed during wound healing helps eliminate pain as tissues heal. Managing acute pain to prevent a more chronic condition postoperatively should be the goal of every practitioner. Mechanism-specific pharmacologic therapy that reduces the intensity and duration of inflammatory nociceptive activity during healing characterizes good medicine (Turk & Okifuji, 2010), (Woolf, 2004).

Analgesics in Surgery

Postsurgical pain management is largely based on inhibition of nociceptive transmission to prevent summation in the CNS and should not interfere with the healing process. Good pharmacologic nociceptive control augments the endogenous anti-nociceptive system that is largely centered in the brain's periaqueductal grey region. Specifically, the pharmacologic goal in pain management is to target the site of peripheral sensitization as efficaciously as possible. This is where the inflammation generates arachidonic acid from cell membrane phospholipids by phospholipase-A2. Arachidonic acid is broken down enzymatically by cyclooxygenase (COX) producing pro-inflammatory lipid compounds known as prostaglandins. Production of prostaglandin cytokines from arachidonic acid is thus referred to as the COX pathway (Vane, 1998). However, there are multiple branches of the COX pathway (COX1 and COX2), and the

COX 2 pathway is known for producing inflammatory chemical compounds while COX1 is known for generating chemical compounds called prostanoids that protect the mucosal lining of the stomach.

Ibuprofen was brought to market in 1969 as a result of searching for a more effective aspirin in the treatment of rheumatoid arthritis (Rainsford, 2003). Since that era, NSAIDs have become the preferred analgesic to modulate the COX pathway (Matoulkova, 2013; Allen, 2009; Mickel, 2006; Sarkar, 2004). Ibuprofen induces analgesic action by non-specifically inhibiting the release of prostaglandins (COX1 and COX2) that result from inflammation. Taken orally, the time of onset of analgesic effect may be between 30 and 60 minutes.

The inflammatory COX2 pathway can be differentiated from the physiologic, constitutive COX1 pathway producing non-inflammatory enzymes. Suppression of cytoprotective enzymes yielded in the COX1 pathway by NSAIDS like ibuprofen may cause gastrointestinal (GI) bleeding, as well as other less common side effects like altered GI motility. Analgesics that exclusively target the COX2 pathway affect specific peripheral neurogenic receptors for effective analgesia without the potential side effects of suppressing the COX1 pathway (Woolf, 2004). Recent animal studies of tolafenamic acid report the NSAIDs to cross the blood brain barrier, thereby possibly targeting central COX receptors located in the brain as well (Subaiea, 2011). However, chronic use of COX2 specific inhibitors led to increased incidence of cardiovascular adverse events such as myocardial and cerebral infarction (FDA Website, 2005). Celecoxib is one of the few remaining COX2 selective inhibitors remaining on the market due to safety concerns with Valdecoxib and Rofecoxib. Despite the pros and cons of nonspecific COX

inhibitors, ibuprofen remains the preferred NSAID to modulate the COX pathway by patients (Matoulkova, 2013; Allen, 2009; Mickel, 2006; Sarkar, 2004), but it is merely one of many NSAID formulations. IV or IM ketorolac tromethamine (KT), which has been safely used for over 20 years as a parenterally administered analgesic, has yet to be shown to have greater efficacy than PO ibuprofen (Wright, 1994 & Braaten, 2014).

Opioid analgesics affect different anti-nociceptive mechanisms than do NSAID analgesics. They have long been used in surgery to manage acute pain because they minimize the onset of central sensitization. The CNS actions of opioid analgesics provide pain control as well as their adverse side effect profile. On the other hand, because NSAIDs control pain through modulation of peripheral nociceptive input induced by acute, inflammatory insult, they do not induce the same centrally mediated adverse side effects.

Opioid analgesics act directly on pain-modulating receptors at the second and third order neurons of in the central nervous system. They also cause nausea, constipation, threaten respiratory depression, and are strongly addictive (Goodsell, 2005). Overuse of opioid analgesics results in tolerance and over time increased dosages are required to achieve the same analgesia. This increased dosing may exacerbate the non-analgesic side effects (Goodsell, 2005). Buckenmaier (2012) describes morphine as effective for managing pain and as the standard against which other analgesic medications are compared. However, he also concedes that when opioids are the sole source of pain management, there are undesirable side effects, such as sedation, nausea, vomiting, ileus, respiratory depression may be exacerbated by continued opioid use (Buckenmaier, 2012). The impetus for opioid administration by practitioners may stem

from patients reporting insufficient analgesia by NSAIDs. Practitioners may thus prescribe opioid analgesics as a means to enhance pain control during wound healing because poorly managed pain following trauma or surgery has a negative impact on all organ systems (Joshi & Ogunnaike, 2005).

Depending on the clinical setting, practitioners may elect to deliver analgesics orally or parenterally (other than orally). Analgesics may be injected via intravenous (IV) or intramuscular (IM) routes, or they may be administered to be absorbed via intranasal, sublingual, or cutaneous (through the skin) routes. For example, Paech, Lim, Banks, Rucklidge and Doherty (2003) evaluated the efficacy of intranasal fentanyl in 23 patients recovering from gynecological surgery. The results revealed rapid onset of analgesia (within five minutes) by absorption of fentanyl through the nasal mucous membranes. However, when queried on preferred route of administration, ten patients preferred IV, seven preferred IN and six did not have a preference.

A significant relationship between the immune system and opioid use may exist. Opioids frequently relied upon to manage pain may be immunosuppressive (Sacerdote, 2006; Budd, 2006; Beilin & colleagues, 2003). The complex multi-factorial immune response following surgery is affected by tissue damage, anesthesia, postoperative pain, and psychological stress (Beilin & colleagues, 2003). Bedesovsky and Del Rey (1996) suggested that because the immune and nervous systems communicate bi-directionally, the nature of pain management might influence the immune response to surgery. In a randomized controlled trial, Beilin and colleagues (2003) evaluated cytokine response to analgesics following abdominal surgery in 115 participants who received one of three pain-modulating modalities:

- (1) pethidine (opioid) intramuscularly (IM)
- (2) morphine (opioid) intravenously (IV)
- (3) 0.1% bupivacaine (local anesthetic) plus epidural fentanyl (opioid).

Participants in Group 3 experienced the least amount of pain and patients in Group 1 reported the greatest amount of pain on the visual analog scale (VAS) up to 48 hours following surgery. The lymphocyte proliferative response was most suppressed in Group 2 and least suppressed in group 3. Production of proinflammatory cytokines from the interleukin (IL) family, namely IL-1B and IL-6, was increased in the first 24 hours following surgery in groups 1 and 2 compared to group 3. The authors suggested the best pain control and most attenuated immune effect observed in group 3 may be attributable to the use of the local anesthetic bupivacaine in combination with epidural fentanyl. Only local anesthesia blocks peripheral nociceptive input from reaching the CNS, and therefore minimizes the potential for central sensitization and central inflammatory/immune changes.

The elaboration of IL-1B during immune responses has been associated with acute, inflammatory, adaptive pain postoperatively. The COX-2 pathway can be induced by IL-1B to produce of more prostaglandin E2 (PGE2) and provoke cascading levels of pro-inflammatory cytokines like substance-P and nerve growth factor (Safie-Garabedian, 1995). Increased pro-inflammatory cytokines may contribute to more severe pain and more severe pain may contribute to increased pro-inflammatory cytokines (Watkins, 1995). Nociceptive barrages on the CNS and peripheral nerve damage activates glia cells, which increase the production of pro-inflammatory cytokines in the central nervous system. Increased pro-inflammatory cytokines lead to neuro-inflammation which can

perpetuate chronic or neuropathic pain in the late postoperative period (Sweitzer, Colburn, Rutkowsky & DeLeo, 1999; DeLeo & Yezierski, 2001).

Strategies to Reduce Postoperative Pain with Preoperative Medication

In a review, Jackson, Moore and Hargreaves (1989) recommended following the same regimen (400 mg ibuprofen 30 minutes prior to the procedure). They suggested that ibuprofen's superior analgesic effect might be due to inhibition of prostaglandin synthesis at the site of tissue insult. Decreasing subsequent localized inflammation and preventing sensitization to pain producing cytokines such as histamine and bradykinin is the predominant mechanism of action (Jackson, 1989).

Pain Management Techniques in Periodontal Surgery

Periodontal surgery involves the elevation of tissue flaps from the jawbone, or the harvesting of tissue from one site in the mouth to be grafted at another location in the mouth. These procedures induce inflammatory mechanisms that elicit acute pain and require sound postoperative pain management. Curtis and McLain (1985) evaluated 304 participants to quantify pain and postoperative complications following one of three types of periodontal surgery:

1. soft tissue surgery
2. osseous surgery
3. mucogingival procedures.

In total, 210 (69%) of the participants reported having some degree of pain (minimal (n)=62, moderate (n)=134, severe (n)=14). Linear regression models were computed to determine the association between a particular variable and pain. Using regression variable coefficients, when mucogingival surgery involved tissue grafts from one location

that are transplanted to another location was 3.5 times more postoperative pain relative to osseous surgery and 6 times more pain than soft tissue surgery. They also noted the duration of surgery significantly correlated with postoperative complications and pain.

Mucogingival periodontal surgery encompasses a spectrum of procedures, including soft tissue autografts, allografts and xenografts. Autografts involve harvesting donor tissue from one site in the oral cavity and transplanting to a second surgical site in the oral cavity of the same patient. Examples of autografts are soft tissue from palate transferred to around teeth to rebuild gum tissue or bone harvested from ascending mandible that is placed at a site where disease or trauma has caused a loss of bone. Allografts use donor tissue from other humans and xenografts use tissue from animals. These grafts placed at recipient sites negate the need for donor site surgery.

Griffin, Cheung, Zavras and Damoulis (2006) compared the frequency of complications with soft tissue autografts to allografts. One week following surgery a survey documented pain, swelling and bleeding. 371 autografts performed by a single operator on 228 participants were evaluated. Duration of the procedure and smoking were associated with increased severity of postoperative complications. Free soft tissue autografts (FTG) from the palate that harvest both the epithelium and underlying connective tissue, and heal by secondary intention caused more bleeding and complications than connective tissue autografts (CTG) that only harvest underlying tissue. Allografts were associated with reduced swelling and bleeding. This study was not randomized and examiners were not blinded.

Wessel and Tatakis (2008) compared patient-based outcomes for CTGs and FTGs. Twenty-three participants (12 CTGs and 11 FTGs) completed questionnaires at

three days and three weeks after surgery to assess postoperative pain, number of analgesic pills taken, and number of days pills were taken. Postoperative pain was assessed using VAS. Three days following surgery, the difference in pain level between the two groups was not significant; however, a significantly more FTG patients reported pain in the palate (donor site). There was no statistically significant difference between groups in terms of the number of pills taken or the duration of analgesic consumption. For both groups, the total number of pills taken correlated significantly with the level of pain reported at three weeks following surgery. Average use of 600 mg of ibuprofen during the first three postoperative days was 8.6 pills for CTG patients and 11.1 pills for FGG patients.

Rashwan (2009) compared acetaminophen 500 mg with 30 mg caffeine to ibuprofen 400 mg in pain management following periodontal surgery. This prospective randomized, double-blinded crossover clinical trial involved 15 participants who received open flap debridement at two quadrants with three weeks between surgeries. Scheduled dosages of the analgesic were given immediately following surgery and eight hours after the first dose. Pain was monitored during the first eight hours and on the following day using the 101-point Numeric Rate Scale (NRS-101) (McCaffery 1999) and using the four-point Verbal Rate Scale (VRS-4) (Portenoy 1996). Because of the efficacy observed, Rashwan anecdotally concluded that acetaminophen 500 mg with caffeine 30 mg may be indicated in patients with gastric ulcers or bleeding tendency (not observed or measured) as an effective alternative to ibuprofen. VAS was reported to be difficult for patients to comprehend in the pilot study by Rashwan. However, a literature review of these three most commonly used scales indicate that they are all valid and accurate for

clinical research (Williamson, 2005). The review indicated that patients tend to prefer the VRS (Williamson, 2005), but the NRS-101 may have the best sensitivity and can generate data that is amenable to statistical analysis (Williamson, 2005).

Ketorolac Tromethamine to Manage Pain

Since Food and Drug Administration (FDA) approval in 1989, KT has been used to manage pain by many medical specialties using various routes of administration such as IV or IM.

Ben-David (1996) sought to determine if NSAIDs, delivered through varying routes of administration, were useful in conjunction with regional anesthesia. Preoperatively, 30 mg KT was administered by one of the following routes: IV, IM, PO or intrawound (IW) to 70 participants undergoing outpatient inguinal hernia repair. All patients were given ilioinguinal nerve and field blocks preoperatively. Postoperative pain levels and analgesic requirements were equally reduced for the IM, IV and IW groups compared to PO, which was superior to control.

The use of corticosteroids and postoperative administration of IV KT effectively reduced both pain and inflammation following third molar surgery (Dionne, Gordon, Rowan, Kent, and Brahim, 2003). This clinical study evaluated inflammatory cytokine levels (TXB2, PGE2) in the first 60 minutes postoperatively. Patients who received 8 mg dexamethasone PO and IV before surgery, plus 30 mg ketorolac at pain onset exhibited significant decreases in TXB2 and PGE2 levels, and concomitantly, decreased pain levels compared to placebo. Administration of KT resulted in a rapid analgesic response and significantly better analgesic effect than groups that did not receive KT.

Intranasal Ketorolac

IM administration of 30 or 60 mg of KT demonstrated “highly effective analgesia” but PO administration of KT was approved only in 10 mg dosages due to gastrointestinal irritation (Rubin, 1990). Ten mg of PO KT was insufficient to alleviate severe pain. Given the ineffective nature the KT given PO and the efficacy use of IM and IV KT in post-surgical pain management, pharmaceutical researchers began investigating patient self-administration of KT via an intranasal (IN) formulation.

Santus and colleagues (1993) were the first to publish work on the development of an effective nasal formulation of KT. Using a rabbit model, evaluation of four formulations *in vitro* and *in vivo* revealed that a 5% solution of KT containing 0.3% sodium glycolate “enhancer” (IN_e) allowed the best mucosal absorption. The IN_e method of administration (initial peak concentration of $3,200 \pm 1,100$ ng/ml) also provided a controlled release that doubled the apparent half-life compared to IV formulation (IN_e t_{1/2} ≈ 90 minutes). Delivering KT via IN_e resulted in greater than 80% bioavailability (sum mean plasma concentration over five hours) compared to IV administration (initial peak concentration of $14,500 \pm 2,000$ ng/ml). Histological analysis of the nasal turbinates, larynx, and pharynx after eight days of twice daily IN administration revealed changes only in the submucosa of the anterior turbinates. These changes were characterized as acute inflammation in 2 of 3 cases, slight to moderate edema in 2 of 3 cases, and slight to moderate hemorrhage in 3 of 3 cases. In the control and placebo rabbit the same inflammation and edema changes were seen, but with less frequency, only in the submucosa of the anterior turbinates. Hemorrhage was not seen in the controls and

placebos. The authors concluded that the formulation produced very mild irritation to the nasal tissues.

Further research into nasal mucosal delivery of KT established the groundwork for justifying human clinical trials of IN KT. Quadir, Zia and Needham (2000) assessed pharmacokinetic profiles in rabbit nasal mucosa following a series of spray and powdered formulations. The spray formulation produced significantly better absorption than the powdered formulation and demonstrated an absolute bioavailability of 91% and plasma concentrations comparable to that of IV administration within 30 minutes. Sankar and Mishra (2003) were the first to report on the development of the gelatin microsphere. They subsequently recommended human *in vivo* studies after observing tissue responses in an *ex vivo* study of rabbit small intestine mucosa following sustained IN systemic delivery of KT. Chelladurai, Mishra and Mishra (2008) used *in vitro* and *in vivo* rat muocsa models and showed that KT muco-adhesive gel caused negligible irritation compared to controls. Nagda, Chotai, Nagda, Patel, and Patel (2011) studied sheep nasal mucosa *in vitro* and *ex vivo* microsphere KT carrying systems and also showed that irritation to mucosa was negligible compared to controls. They also failed to find any severe mucosal damage following prolonged-release of IN KT.

Following the IN KT animal models, clinical trials for FDA approval for human were first published in 2007. McAleer, Majid, Venables, Polack and Sheikh (2007) conducted phase I study using a single dose, crossover, randomized study design. Fifteen healthy participants received open-label 15 mg or 30 mg IM KT, and at separate occasion a blinded, randomized 15 mg or 30 mg dose of IN KT. Participants were admitted to the Clinical Unit at Medeval Limited Manchester Dosing for 24 hours before being was

administered study doses. Blood samples indicated the relative bioavailability of IN KT was 67% to 75% (15mg and 30mg respectively) compared to IM KT. The investigators concluded that IN administration offered a therapeutic alternative to IM administration.

Phase II and III clinical trials in 2008, 2009 & 2010 studied the safety and analgesic efficacy of IN KT in managing postoperative pain using randomized, double-blinded, placebo-controlled methodology. Phase II evaluated pain levels for 127 participants undergoing unspecified “major surgery” using VAS over a 48-hour postoperative period, and calculated summed pain intensity differences (SPID). PID is calculated by subtracting the post-dose score from the baseline score. Then SPID is computed by taking a weighted sum of the PID scores at the given time intervals and normalizing data to account for differences in varying baseline pain levels amongst participants (Farrar, Portenoy, Berlin, Kinman, Strom, 2000). Phase II data showed that participants who received 30 mg IN KT consumed significantly less morphine during the observation period and experienced less pyrexia and tachycardia. SPID at four and six hours were significantly larger compared to placebo after receiving 30 mg IN KT (Moodie, Brown, Bisley, Weber and Bynum, 2008).

Two phase III clinical trials evaluated efficacy and tolerability of IN KT in abdominal and orthopedic surgery patients in 2009 (Brown, Moodie, Bisley & Bynum, 2009 & Singla, Singla, Minkowitz, Moodie & Brown 2010). The first Phase III trial randomized three hundred participants (N=199 KT, N=101 placebo) following hysterectomy and hip replacement surgery. This Phase III study reported results consistent with Phase II, with 34% less overall morphine intake following IN KT (31.5mg), and increased SPID at six hours following IN KT administration. Morphine

use in the first 24 hours was reduced by 20% and 50% at various time points for the KT group compared to placebo ($p=0.004$) (Brown, Moodie, Bisley & Bynum, 2009).

In the second Phase III trial (Singla, Singla, Minkowitz, Moodie & Brown 2010), participants were randomly assigned to receive 31.5 mg KT ($n=214$) or placebo ($n=107$) every six hours after surgery for 48 hours, and then four times per day up to five days. The primary efficacy measure was SPID after six hours, and secondary efficacy measure was the quantity of morphine consumed after 72 hours. The high efficacy and convenience of IN dosing suggested that IN KT might have usefulness in ambulatory care settings (Brown, Moodie, Bisley & Bynum, 2009). Investigators concluded that IN KT was well tolerated, provided effective analgesia within 20 minutes, and reduced opioid analgesia consumption (Singla, Singla, Minkowitz, Moodie & Brown 2010).

The recommendations by Singla, Singla, Minkowitz, Moodie & Brown (2010) were reinforced by Grant and Mehlisch (2010) who evaluated the efficacy of a single 31.5 mg dose of IN KT immediately following oral surgery. Patients were evaluated at 20, 40, 60, 90 and 120 minutes, and then hourly until, 8 hours after the dose. This study was supported by the manufacturer of SPRIX® (Ketorolac Tromethamine nasal spray), Roxro Pharma, and was conducted between 2003 and 2005, prior to FDA approval of SPRIX® in 2010. The SPID was significantly higher in the KT group compared to placebo. A larger percentage of the KT group reported good, very good, or excellent pain control compared to placebo (60% vs 13%). Times to perceptible (21.5 minutes) and meaningful (60 minutes) pain relief were significantly shorter, and time to rescue analgesic was significantly longer in the KT group ($p<0.001$).

Considering the abuse and misuse of opioids, and postoperative problems related

to opioid use, Snyder and Bregmen (2012) reviewed the literature and presented the use of IN KT as a safe and viable alternative. They indicated that the top three adverse events related to use of SPRIX® were nasal discomfort (15%), rhinalgia (13%) and increased lacrimation (5%). Concomitant use of SPRIX® with other medications may be safe and applicable in some situations.

The FDA approved SPRIX® by Roxro Pharmaceutical's on May 14, 2010 for the management of moderate to severe pain. Boyer, McDonald and Zoctis (2010) described the pharmacokinetic profile of IN administration in a study that evaluated local tolerance and systemic toxicology in rats and rabbits. Administration of IN SPRIX® exhibited toxicity similar to that of other routes of administration, and did not result in adverse effects of the nasal passage, upper or lower respiratory system.

Guidance concerning the use of IN KT in terms of onset, duration and contraindications (Med Lett Drugs Ther, 2012), its pharmacological properties, clinical efficacy and tolerability in short-term management of pain (Garnock-Jones, 2012) has been published. Analgesia occurs in 20 minutes, reaches peak in about 45 minutes, has duration of about five hours and the half-life elimination is between five and six hours, which is similar to IM administration. SPRIX® is FDA approved for short-term (up to five days) treatment of moderately severe pain in adults. It is not recommended for longer use due to gastrointestinal toxicity. Pregnancy risk is C (risk cannot be ruled out) before 30 weeks of gestation and D (positive evidence of risk) when used beyond 30 weeks gestation, which is the same as ibuprofen. Since it reduces the effectiveness of angiotensin converting enzyme inhibitors and angiotensin receptor blockers, KT should be administered with caution in patients who use angiotensin receptor antagonists. It also

increases the toxicity of methotrexate by decreasing renal clearance and prostaglandin synthesis. , KT is contraindicated in those with severe renal impairment because of its renal metabolism (Med Lett Drugs Ther, 2012).

Bacon, Newman, Rankin, Pitcairn and Whiting (2012) investigated the synthetic macromolecule Tc-diethylenetriaminepenta acetic acid (Tc-DTPA) to create a radiolabeled SPRIX® formulation (31.5 mg). This radiolabeling enabled testing the deposition of IN KT in the lungs of healthy participants following nasal inhalation of different intensities (gentle versus vigorous sniff) and under different postural conditions (upright or semi-supine). It also facilitated describing the deposition pattern of IN KT solution in the nasal cavity while monitoring its clearance from the nasal tissues over a six-hour period. The majority of the dose was deposited in the nasal cavity. The fractions of the dose observed in the lungs were less than 0.5% and were determined to be scattered radiation instead of true pulmonary deposition. The fraction observed in the pulmonary tissues was not affected by posture or inhalation maneuvers; but the most uniform distribution of the radiolabeled IN KT was observed with participants in the upright position. Clearance rates were very rapid, with only 16% to 30% of the dose remaining 10 minutes following administration, and 6% to 14% remaining after six hours. The authors concluded that in order to maximize the amount of drug deposited and retained in the nasal cavity, patients should inhale gently in the upright position.

Two additional studies evaluating the use of IN KT in the dental setting were recently added to the literature. Maroli and colleagues (2014) repeated the protocol reported by Turner and colleagues (2011) with 20 patients being treated for moderate to severe endodontic pain. The results were the same as those reported by Turner and

colleagues (2011) with significantly better pain relief compared to placebo at 30 minutes and 4 hours following the first intranasal dose. Bockow and colleagues (2013) evaluated pain following titanium dental implant surgery and the efficacy of IN KT as a means of pain management during the entire postoperative healing period. Eighty nine percent of the 25 participants reported moderate to severe pain following dental implant surgery and 56% of the participants required analgesic dosing of IN KT up to three days. Thirty six percent of the participants reported “brief stinging” of the nasal mucosa upon administration, but the medication was overall tolerated well (Bockow, Korostoff, Pinto, Hutcheson, Secreto, Bodner, Hersch, 2013).

Off Label Uses of Intranasal Ketorolac

Although the primary indication of IN KT is to manage short-term (five days) moderate to severe pain, aerosolized KT may be administered PO as an off label use for the diagnosis and treatment of aspirin-exacerbated respiratory disease (AERD). AERD also refers to aspirin induced asthma, observed in patients who demonstrate Samter’s triad: asthma, aspirin or NSAID sensitivity and nasal polyps. AERD is typically managed by avoiding COX1 inhibitors, or by aspirin-desensitization, which is a method to reduce asthma symptoms and delay the growth of nasal polyps by incrementally increasing metered dosing of aspirin until 325mg are administered.

The first study to evaluate AERD using IN KT was done by White, Bigby and Stevenson (2006) was performed before the FDA approved of SPRIX®. Injection preparations of KT vials (60mg/ml) were diluted into preservative-free isotonic sodium chloride and delivered via Nasacort AQ spray bottle. The investigators sought to determine if IN KT nasal challenge demonstrated acceptable specificity and sensitivity

for diagnosing AERD in 29 symptomatic participants. Following challenge with 2.1, 5.2 and 7.8 mg IN KT, sensitivity was 78% and specificity was 64%. Mild bronchospasm occurred in three of the participants, two of whom received higher starting doses of KT (7.8mg and 5.2mg). The authors concluded that IN KT administration is an accurate and safe method for diagnosing AERD. A review of 614 studies reported that aspirin desensitization would significantly improve quality of life by reducing nasal polyps, decreasing the number of sinus infections, and reducing the need for systemic corticosteroids and sinus surgery in patients with AERD (Xu, Sowerby, Rotenberg, 2013).

Only recently did investigators attempt to use IN KT desensitization in the treatment of AERD in lieu of aspirin desensitization. In a study by Lee and colleagues (2010) of 100 suspected patients (aged 18-73 years) with AERD, four increasing doses (1.26mg to 7.56mg) of IN ketorolac were given at 30-minute intervals initially. Afterwards patients were given PO aspirin challenge (60mg followed by additional dosing up to 325mg depending on the reaction). Respiratory parameters such as forced expiratory volume in 1 second (FEV₁) and peak nasal inspiratory flow (PNIF) were monitored following the challenges. They concluded that IN KT challenge and desensitization followed by rapid oral aspirin challenge is effective, safe and less time-consuming than standard oral aspirin desensitization. Chang, Chin and Simon (2012) recently reviewed the IN KT desensitization protocol and discussed possible sequelae. Possible reactions following the IN KT challenge included naso-ocular symptoms, such as watery eyes, runny nose, sneezing, itching nose, FEV₁ decline, laryngospasm, hives, flushing, gastric pain, or hypotension (Chang, Chin and Simon, 2012).

Intranasal Ketorolac Use with Adolescents

Drover, Hammer and Anderson (2012) characterized the pharmacokinetics of a single intranasal dose of ketorolac in 20 adolescent patients following surgery (orthopedic, general and cardiothoracic) as being well tolerated with minimal adverse effects. Using a 1-compartment model with a first-order time-concentration profile to describe the absorption and elimination of IN KT, the drug is distributed into the equivalent of a single volume, and then eliminated at a constant, predictable rate. IN KT administration rapidly increases the plasma concentration such that it is a therapeutic alternative to IV injection.

A review of the literature revealed that IV KT might be effective in treating adolescent migraine. Bailey and McManus (2008) conducted a qualitative systematic review of 15 randomized controlled trials evaluating the treatment of migraines in children. They concluded from the review that prochlorperazine (antipsychotic agent) was more effective than IV ketorolac in relieving pain at one hour.

Modified SPRIX® for Migraine

Recent research evaluated a modified formulation of SPRIX® containing 6% lidocaine (ROX-828) for the treatment of migraine with and without aura (Pfaffenrath, 2012). Randomly assigned, 140 participants (95% women, aged 19-60 years) with migraine self-treated with 31.5 mg IN ketorolac with 6% lidocaine or placebo with 6% lidocaine. Participants in the experimental group showed significant improvement in pain relief compared to placebo at all times, with the exception of 0.5 hours and 24 hours ($p<0.05$). Nearly 20% more participants in the experimental group achieved a pain-free

status compared to placebo ($p<0.05$). The evidence from this study suggested the ROX-828 was well tolerated and that a single dose may be effective in reducing migraine pain.

Summary

Advancements in scientific research of the nociceptive system as it relates to the immune system afford practitioners the ability to target specific physiologic processes. Such therapy minimizes postoperative pain during the wound healing process that is caused by acute inflammation and tissue insult. A wide variety of opioid and non-opioid analgesic medications, some of which have been proven more efficacious than others, are available in the management of postoperative pain. SPRIX® has been shown to be an effective postoperative NSAID analgesic for patients experiencing pain from general surgery, and is also recommended as an adjunct to pain control in an outpatient setting (Brown et al 2009, Singla et al 2010, Grant et al 2010, Turner et al 2011, Bockow et al 2013). Dental research is replete with studies evaluating the efficacy of pain management with preoperative analgesic medication in patients undergoing third molar surgery. However, there are few studies considering the effectiveness of preoperative analgesic medication in periodontal flap surgery. Compared to third molar extractions, some periodontal procedures may induce a greater generation of inflammatory cytokines due to:

1. the increased duration of surgery
2. dimensions of surgical flaps,
3. manipulation of soft and hard tissues in the surgical field.

The medical and dental literature demonstrates effective use of the most recently FDA-approved NSAID formulation, IN KT, in well controlled randomized trials. Use of

this novel formulation is documented in extraction of third molars in order to determine time to pain onset postoperatively, and in endodontic therapy as an adjunct to anesthesia in patients with acute infection. But the number of studies evaluating the use of IN KT as an adjunct to pain control in the dental setting is limited. Effective control of the nociceptive inflammatory cytokine pathway during surgery may prove to be the best means of minimizing the administration of opioid analgesics on a routine basis. While administration of preoperative NSAID appears to be predictable, the difference in effectiveness and duration of nociceptive inflammatory cytokine modulation to reduce pain between PO Ibuprofen and IN KT is unknown. Pain management for extensive periodontal surgery often use pre-operative NSAID with post-operative NSAID and opioids. Dental research has yet to evaluate in highly painful procedures, such as quadrant periodontal flap surgery, the effect of preoperative administration of IN KT on postoperative dental pain levels and assess the effect on post-operative NSAID and opioid consumption. Hence, the purpose of this study will be to evaluate the effectiveness of preoperative administration of IN KT compared to placebo in periodontal flap surgery in terms of postoperative pain control and NSAID/opioid consumption. The specific aims of the investigation will be:

1. Determine the effect of a single 31.5 mg dose of IN KT compared to a placebo on postoperative analgesic consumption during the initial five postoperative days when given 20 minutes prior to a procedure in patients undergoing periodontal flap surgery.
2. Determine the effect of a single 31.5 mg dose of IN KT compared to a placebo on postoperative pain levels during the initial five postoperative days when given 20 minutes prior to a procedure in patients undergoing periodontal flap surgery.

CHAPTER III: MATERIALS AND METHODS

Focused Question

A focused question was developed. In patients undergoing periodontal flap surgery, what was the effect of a single 31.5 mg dose of IN KT compared to a placebo on postoperative pain and analgesic consumption during the initial five postoperative days when given 20 minutes prior to a procedure?

Literature Review

Comprehensive review of the literature was performed using PubMed-MEDLINE database to identify appropriate studies as they relate to analgesic control before, during, and after periodontal and oral surgery. Key search terms included “etiology and genesis of postoperative pain in surgery” and “postoperative pain periodontal surgery” and “preemptive analgesia and postoperative pain in surgery” and “ketorolac tromethamine and SPRIX”.

Following comprehensive review of the literature, use of human subjects to accomplish the goals of the study was justified. The proposed project aimed to not only validate the concept of preemptive analgesia observed in previous human research, but also evaluate the use of a novel analgesic in the periodontal surgery outpatient setting. The use of human subjects was essential for this project. Data was to be collected through the use of randomized intervention that would not impact the outcome or standard of care in the periodontal surgery clinic. Findings from these observations could demonstrate the ability to enhance preemptive analgesia more so than oral formulations of non-steroidal analgesics.

Study Design

This study was designed as a blinded randomized parallel-arm controlled clinical

trial. Participants and surgical providers were to be blinded to the status of the participant's pre-operative analgesic status: intervention (labeled "A") or control (labeled "B"). Bottle A would have standard FDA approved IN KT otherwise distributed as SPRIX®. Bottle B would have placebo as provided by Roxro pharmaceuticals. Prior to the surgical procedure, the surgical team would open an envelope with a card labeled "A" or "B" and allow the participant to administer the contents of the bottle as appropriate.

Subject Population

The population to be included comprised male and female patients aged 18 years and older with the diagnosis of periodontal disease consistent with needing periodontal flap surgery such as mucogingival deformities around teeth, gingival recession, localized or generalized chronic or aggressive periodontitis. Patients requiring periodontal flap surgery would receive one of the following procedures: subepithelial connective tissue autograft, free gingival graft, guided tissue regeneration or osseous respective surgery. Participants were required to meet health eligibility requirements and not have any conditions that will exclude them from the study (see exclusion criteria below). Females of reproductive age were asked to submit urine samples for pregnancy testing prior to surgery. Urine HCG tests was to be conducted in the Department of Periodontics in accordance with WRNMMC Bethesda Point of Care Testing Procedures. Pregnant and nursing females would be excluded from this study to prevent the possibility of any harmful effects to the fetus/infant during treatment. Periodontal surgery is routinely deferred until pregnancy is over.

Any patient eligible for military healthcare benefits, age 18 years or older, referred to the Naval Postgraduate Dental School (NPDS) Periodontics Department for

periodontal flap surgery is indicated would be eligible to enroll. Since beneficiary care at WRNMMC Bethesda is based on clinical need, and periodontal disease affects all ethnic populations and all demographic categories (Hancock et al. 1981), subject selection was anticipated to be equitable.

Inclusion Criteria

- a. Patient aged ≥ 18 years old
- b. Patient planned to receive periodontal flap surgery involving multiple tooth flap reflection, mucogingival surgery with flap repositioning, such as subepithelial connective tissue autograft, free gingival autograft, or guided tissue regeneration, or osseous resective surgery involving flap reflection.

Exclusion Criteria

- a. Patient under the age of 18
- b. Patients with periapical pathology, unrestored caries, defective restorations, root resorption, or vertical root fracture
- c. Female patients who are pregnant or nursing (verified by HCG sample day of surgery)
- d. Patients who currently smoke tobacco or use tobacco products. Former smokers will be excluded if they quit smoking < 6 months prior to selection in the study.
- e. Patients with clinically significant systemic diseases, which may affect healing (e.g. uncontrolled diabetes).
- f. Patients allergic to chlorhexidine gluconate (Peridex).

- g. Patients with known hypersensitivity or history of asthma, uticaria, or other allergic-type reactions to aspirin, ketorolac, other NSAIDs or EDTA
- h. Patients with poor oral hygiene unsuitable for periodontal surgery
- i. Patients who cannot or will not sign the informed consent form
- j. Patients receiving immunosuppressive therapy such as chemotherapy and systemic corticosteroids not to include inhaled or topical steroids
- k. Patients with severe endocrine-induced bone diseases (e.g. hyperthyroidism, altered parathyroid function)
- l. Patients with bleeding complications (e.g. hemophilia)
- m. Patients on warfarin therapy
- n. Patient with a history of osteoporosis or taking bisphosphonate medications
- o. Patients with a history of radiation therapy in the head and neck area
- p. Patient requiring intravenous sedation

Procedures

40 subjects diagnosed with periodontal disease or conditions requiring flap surgery for correction would be enrolled in the study. The findings of the comprehensive periodontal evaluation such as probing depths (PD), clinical attachment levels (CAL), and recession would have been recorded on the Navy Periodontal Chart Form - NAVMED 6660/2 by the subject's provider. A study investigator would initiate the informed consent process.

Initial Sequence:

1. Patient is referred for a comprehensive periodontal evaluation.
2. Based on the evaluation, a treatment plan will be developed for each patient. Typical treatment plans are:

- a. Maintenance therapy. No surgical treatment required, patient is not a candidate for the study.
- b. Surgical treatment indicated, but periodontal flap surgery is not indicated, the patient is not a candidate for the study.
- c. Periodontal disease or condition is present and periodontal flap surgery is the treatment of choice.
 - I. Patient will be asked if he or she would like to participate in the study and will then be provided a one page brief about the study
 - 1. If the patient consents to be in the study, the therapy will continue as stated below
 - 2. If the patient does not consent to be in the study, surgical therapy will continue as planned by the patient's surgeon.

Randomization Procedure:

- 1. The research pharmacy would maintain custody of the formulations provided by the manufacturer labeled Bottle A or Bottle B (Formulations would be made by the manufacturer and Bottle A would contain SPRIX® and Bottle B would contain Placebo, which would be normal saline with carrier). The research pharmacy would also generate the randomization table and would dispense Bottle A or Bottle B upon receipt of a prescription for "Intranasal Ketorolac vs. Placebo".
- 2. When each participant goes to surgery the investigator would provide the surgical team with the bottle dispensed from the pharmacy.
- 3. The study investigator would record which bottle is administered for each study participant on the data collection sheet.

Surgical Procedure:

Females of childbearing age would be asked to complete a HCG urinalysis prior to the surgical procedure. If the results of the HCG test were positive, the subject would be exited from the study.

At twenty minutes prior to the surgical procedure, the contents of the test or control material would be administered intranasally. Test material would comprise either 31.5 mg ketorolac tromethamine or placebo, dispensed to the surgeon by the research pharmacy, and would be administered with one pump of the bottle into each nostril, and the patient would be advised not to inhale profoundly following administration to allow for the material to lay on the intranasal mucosa. Control material would comprise normal saline with carrier and would be administered in the same fashion with the same instructions to the patient as was given with the test material.

Prior to surgical procedure, in line with standard procedure at the Periodontics Department participants will be anesthetized using local anesthesia (2% lidocaine with 1:100k epinephrine, and/or 4% articaine with 1:100k epinephrine, and/or 3% mepivacaine, and/or 0.5% mepivacaine with 1:200k epinephrine).

The surgical provider would be either a board certified staff periodontist or a 2nd or 3rd year periodontics resident. All surgical providers would be briefed in the protocol. All surgeries would follow the same steps listed below.

1. Surgical set-up is standardized for all surgeries done at the Naval Postgraduate Dental School Periodontics Department.
2. Surgical Procedure Steps:

- a. Administration of topical and local anesthetic at both the recipient and donor sites.
- b. Sulcular incisions and reflection of the surgical flap.
- c. Debridement of the surgical site/defect to remove granulation tissue and calculus using hand instruments and cavitron ultrasonic instrument
- d. Osteoplasty and/or odontoplasty (reshaping unsupported the alveolar bone and/or tooth) will be performed as needed
- e. If a soft tissue graft is being performed, the donor site will be prepared with an initial full thickness incision into the palatal tissue extending parallel to the free gingival margins of the adjacent teeth to obtain sufficient tissue for the recipient site. Full thickness incisions will be made at each end of the initial incision, extending sufficiently to obtain enough tissue for the recipient site. The flap created on the palate will be split parallel and deep to the epithelium to separate the underlying connective tissue. Connective tissue and/or gingival tissue including the epithelium, superficial to the periosteum will be harvested from the site and reduced as necessary to fit the recipient site.
- f. If necessary, root surfaces of the teeth bordering the defect site will be treated with a 24% EDTA gel for 4 minutes. The site will then be washed with sterile saline for 1 minute.
- g. If a soft tissue graft is being performed, connective tissue harvested from the donor site will be placed into the defect up to the level of the cementoenamel junction and will be secured at the site using resorbable

sutures.

- h. If GTR is being performed, the bone graft substitute will be placed into the prepared recipient site and a membrane may be placed as indicated for the procedure.
- i. Primary flap closure achieved at both the donor and recipient sites using a non-resorbable monofilament suture (ie. Gore-tex)
- j. Gauze pressure will be held on the donor and recipient sites for 5 minutes to achieve hemostasis and reduce the size of the fibrin clot formed.
- k. Palatal stent will be placed on the maxilla at the provider's discretion if donor tissue is harvested from the palate.
- l. Periodontal dressing may be placed over the recipient site at the provider's discretion.
- m. Intrasurgical local anesthetic may be administered during the surgery.

Surgeons will annotate the time, type and quantity of anesthetic administered to the patient.

Post-operative Care:

1. All participants would receive the following post-operative regimen:
 - a. Pain medication consisting of any of the following alone or in combination:
 - i. Ibuprofen 800 mg, Take 1 tab PO q6-8h for 72 hours
 - ii. Hydrocodone/Acetaminophen 5/325 mg, Take 1-2 tab PO q6h prn severe/breakthrough pain
 - iii. Oxycodone/Acetaminophen 5/325mg, Take 1-2 tab PO q6h prn

severe/breakthrough pain

- b. 0.12% Chlorhexidine, 1 bottle, Rinse and spit bid with 1 TBSP as directed on the bottle
3. All participants would document the time, type and quantity of medications taken following the procedure.
4. Using the VAS (See appendix A), all participants would document pain levels every 4 hours for the first 12 hours following surgery and then three times daily (morning, mid-day and evening) for 1 week following surgery.
5. All patients would be provided with the standard post-operative instructions.
6. Patients would be recalled at 1 week to assess post-operative healing, remove plaque/deposits on the surgical site, determine pain level, collect VAS worksheets and record quantity of analgesics consumed. Collection of data is terminated at 1 week postoperatively.
7. After the 1-week evaluation, patients would be exited from the study and followed by their primary provider for periodontal maintenance therapy.

Analysis of Data:

1. Pain levels and analgesic consumption quantity would be assessed at the indicated time intervals throughout the week postoperatively and would be compared between groups.
2. Statistical analysis would evaluate intervention and control differences.

CHAPTER IV: RESULTS

Results of Literature Review

A comprehensive literature review using PubMed-MEDLINE identified appropriate studies related to preoperative administration of NSAID analgesic prior to surgery and evaluated the postoperative pain and/or analgesic consumption. Between 1978 and 2013 there were nineteen studies that evaluated postoperative outcomes following preoperative administration of NSAIDs or NSAIDs combined with other medications (Table 1).

Overall findings revealed fourteen studies (74%) concluded that preoperative analgesic consumption reduced postoperative pain, but of the five studies that reported no difference in postoperative pain, only two were placebo controlled (Figure 1). Of the fourteen studies reporting a reduction in postoperative pain, 50% reported concomitant reduction in analgesic consumption, but of the remaining seven studies that did not report reduced analgesic consumption four were not measured and one was not placebo controlled (Figure 2).

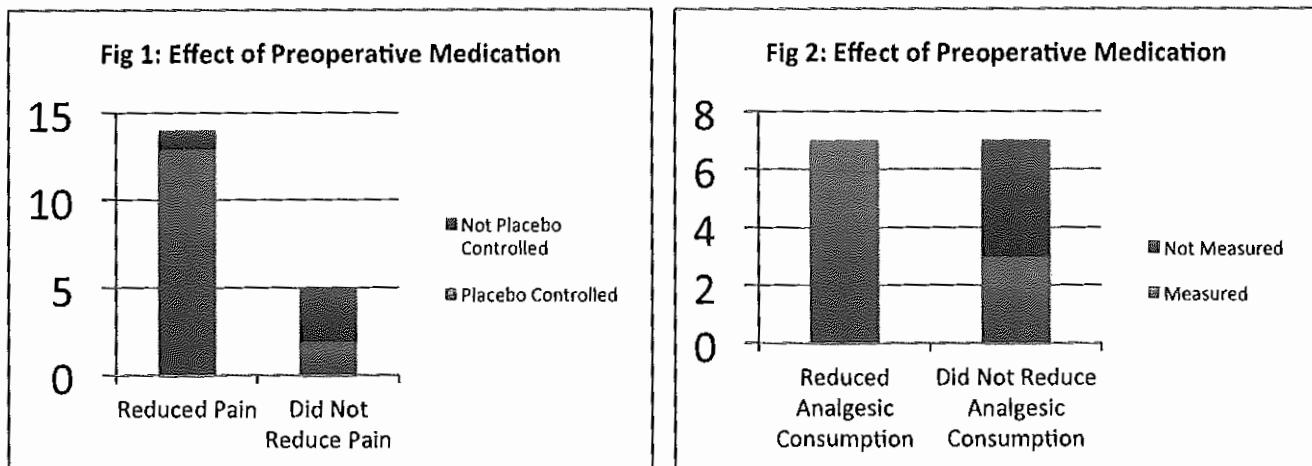
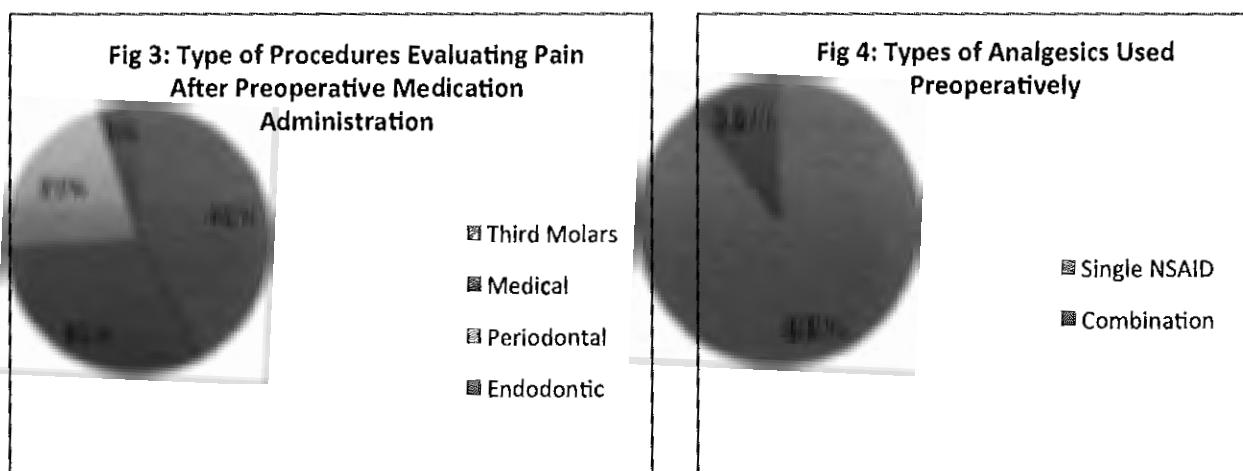


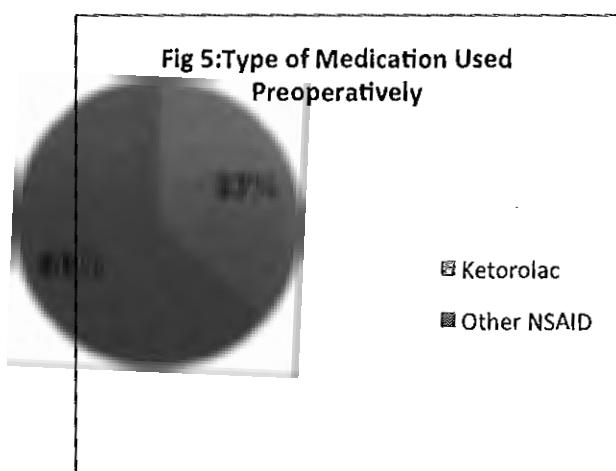
Table 1: Selected studies that evaluated postoperative outcomes following preoperative administration of NSAIDs

Author	Year	Preoperative Medication/Intervention	Procedure Type
Dione	1978	ibuprofen, placebo	Third molars
Higgins	1994	ibuprofen, ketorolac, control	Laparoscopic Tubal Ligation
Chui	1995	diclofenac, ketorolac	Laparoscopic Sterilization
Mather	1995	paracetamol, paracetamol and ketorolac, morphine	Tonsilectomy
Zacharias	1996	diclofenac, methadone	Third molars
Trombelli	1996	ketorolac, placebo	Perio Flap Surgery
Tucker	1996	etodolac, acetaminophen and codeine	Osseous Surgery
Mixter	1998	ibuprofen, ketorolac	Laparoscopic Hernia Repair
Ilkjaer	2000	ibuprofen, dextromethorphan, combo	Gynocelologic Surgery
Pickering	2002	ibuprofen, rofecoxib, placebo	Tonsilectomy
Dionne	2003	dexamethasone and IV ketorolac, dexamethasone and placebo, placebo and placebo	Third molars
Joshi	2004	ibuprofen, diclofenac, paracetamol and codeine, placebo	Third molars
Chiu	2005	ibuprofen, rofecoxib, placebo	Third molars
Steffens	2011	celecoxib, entoricoxib, placebo	OFD
Steffens	2011	entoricoxib, dexamethasone, placebo	OFD
Turner	2011	IN ketorolac	Endodontic
Isiordia	2012	meloxicam, tramadol	Third molars
Trindale	2012	sublingual Ketonolac	Third molars
Bauer	2013	ibuprofen, ibuprofen and dexamethasone, placebo	Third molars

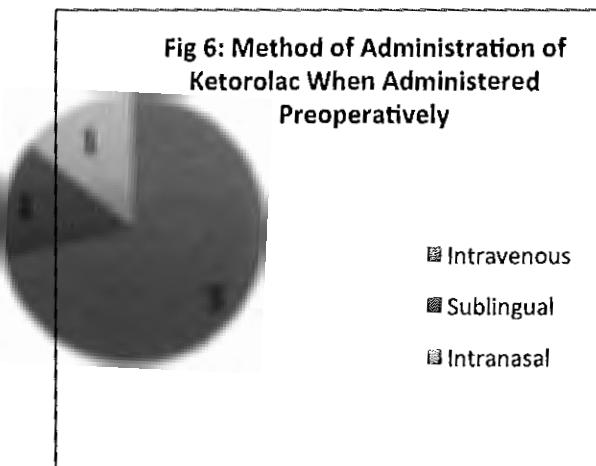
Of the nineteen studies evaluated, the majority of those evaluating the effect of preoperative use of NSAID pain medication on postoperative pain levels were done so after third molar surgery, 32% were in general surgery medical type procedures and only 21% studied its effect in periodontal flap surgery (Figure 3). Nearly 90% of studies evaluating preoperative NSAID administration evaluated the use of a single agent, but 11% of studies evaluated the efficacy of a combination of a single NSAID with another analgesic agent (Figure 4).



Considering the type of medication used preoperatively, 37% of the nineteen studies used ketorolac as the preoperative pain medication and the rest used some other type of NSAID (Figure 5).



Of the seven studies that evaluated the effect of preoperative ketorolac administration, 5 administered intravenously, one administered sublingually and only one administered the pain medication intranasally, and none of these studies evaluated its efficacy in periodontal flap surgery (Figure 6).



Results of Industry Sponsorship

Seven months after the FDA approval of SPRIX® in 2010, Roxro pharmaceuticals signed a binding merger agreement with Luitpold pharmaceuticals, a subsidiary of Daiichi Sankyo. SPRIX® was launched by Regency Therapeutics in May 2011 to actively promote the product in the marketplace. Investigators at NPDS Periodontics Department established initial contact with the chief medical and chief scientific officers of Roxro Pharmaceuticals in the fall of 2012. At this stage, the merger of Roxro and Luitpold Pharmaceuticals was in progress, as the chief scientific and medical officers were operating under titles at Roxro Pharmaceuticals. The chief medical officer offered support by means of providing SPRIX® and placebo to NPDS Periodontics Department for the purpose of evaluating the efficacy in a clinical

setting. During the subsequent 18 months, a double-blinded randomized clinical trial was designed to test the effect of preoperative administration on postoperative pain and opioid analgesic consumption after periodontal flap surgery in an outpatient setting. The double-blinded randomized controlled clinical trial to test the efficacy of administering 31.5mg INKT 20 minutes prior to periodontal flap surgery was designed and reviewed by WRNMMC Department of Research Programs administrative and scientific staff in the spring of 2014. Upon initial review of the study design, contact was reestablished with the chief scientific officer of what had become Luitpold Pharmaceuticals to discuss the logistics of reviewing the protocol, ordering the product and placebo and facilitating transfer to the research pharmacist at WRNMMC. In the fall of 2014, the chief scientific officer of Luitpold Pharmaceuticals notified investigators at NPDS Periodontics Department of a recent decision by the executive management within the company to discontinue active promotion of SPRIX® and sponsorship of clinical trials by means of manufacturing and no longer providing placebo after November of 2014. The reason for this decision was due to an impending arrival of generic INKT on the market in the spring of 2015 (5 years after FDA approval of SPRIX®), and projected lack of strength of SPRIX® relative to the overall Luitpold portfolio.

Upon Luitpold Pharmaceuticals withdrawal of support, the double-blinded placebo controlled clinical trial designed to evaluate the effect of preoperative administration of SPRIX® on postoperative pain and opioid analgesic consumption following periodontal flap surgery was reviewed by NPDS Periodontics Department investigators for financial feasibility without industry sponsorship. One option considered included, purchasing SPRIX® for the study and creating a placebo of IN

normal saline to execute the study. There were two barriers to this course of action. First was the lack of funding within the NPDS Research Department to sponsor purchase of SPRIX® for the study. Second was a lack of access to acquire carrier bottles that could be used to administer placebo. Request was made to the chief scientific officer of Luitpold Pharmaceuticals to purchase empty bottles of SPRIX® with the purpose of administering placebo for the study, but the request was denied. Concerns about executing the study without industry support centered around the inability of the research pharmacist to blind study investigators from intervention and control groups due to unique and patented product materials such as the pharmaceutical carrier and the metered dosing delivery bottle of SPRIX®. Due to these significant challenges, the decision to discontinue the execution of this study was finalized by NPDS Periodontics Department investigators.

CHAPTER V: DISCUSSION

Implications of Literature Review

The literature demonstrates in efficacy comparisons that non-opioid analgesics can provide sufficient postoperative analgesia in many surgical interventions. These positive results are achieved through several pain management techniques, incorporating various analgesics, by different subspecialties of medical practice. For example, Pickering, Bridge, Nolan and Stoddart (2002) demonstrated improved postoperative analgesia without causing an increase of intraoperative complications through the use of preoperative ibuprofen, the non-specific COX inhibitor (Pickering, 2002). The study evaluated the effectiveness of postoperative analgesia from paracetamol (20mg/kg) when either rofecoxib (0.625 mg/kg), or ibuprofen (5mg/kg) or placebo were used as analgesic premedication for tonsillectomy in 98 children aged 3-15 years. The primary outcome variable was the need for early supplementary analgesia within two hours after surgery. The addition of ibuprofen to paracetamol reduced the need for early analgesia from 72% to 38%. The addition of rofecoxib, a COX2 specific antagonist, did not significantly decrease the need for early postoperative medication.

Strategies to Reduce Postoperative Pain with Preoperative Medication

The use of opioid and non-opioid preoperative analgesic medications has been studied for many decades in the literature. The efficacy of preoperative administration of KT compared to ibuprofen for laparoscopic tubal ligations was evaluated in 45 women who were randomized to receive 60mg IV KT, or 800mg oral ibuprofen, or placebo (control) 30 minutes prior to general anesthesia (Higgins, Givogre, Marco, Blumenthal and Furman 1994). Outcome evaluations included pain levels, analgesic requirements,

side effects, and recovery time. Evaluations were made between 15 and 75 minutes following surgery in the post-anesthesia care unit (PACU), at hospital discharge, and 6 and 24 hours following discharge. Results revealed that 80% of control participants required parenteral morphine, compared to 73% of both experimental groups. The differences in quantity of morphine consumption, pain levels reported, fatigue, recovery time, and incidence of postoperative nausea and vomiting between control and intervention groups were not statistically significant. The authors concluded that preoperative administration of KT or ibuprofen did not decrease postoperative pain or side effects in this population. Unfortunately, this study (Higgins, Givogre, Marco, Blumenthal and Furman 1994) did not stratify patients in terms of co-morbidities, meaning that varying levels of central sensitization may have obscured analgesic effects on surgically induced pain between subjects. Further, the study only evaluated outcomes for 24 hours. Even though VAS pain levels (0-100mm scale) were similar during the first 75 minutes, the end of observation observed divergent vectors such that VAS pain levels reported in the control group was 15mm greater than that of the KT group. Given the patients were administered general anesthesia, VAS interpretation during the first 75 minutes also may have confounded by the effects of the general anesthetic agents, during which VAS scores for all groups was nearly identical.

Another study of 70 participants undergoing laparoscopic (minimally invasive) hernia repair assessed outcomes when either 60 mg IV KT or 800 mg PO ibuprofen was administered one hour prior to surgery (Mixter, Meeker and Gavin 1998). All participants received a local injection of 30 ml of bupivacaine before the trocar (an instrument shaped like a hollow cylinder placed to introduce devices used in laparoscopic

surgery) was inserted. Participants were discharged within five hours of the procedure and instructed to take 400 mg ibuprofen every four hours for 24 hours regardless of pain levels. Pain intensity was assessed by VAS at discharge and pain outcomes were assessed by a standardized telephone questionnaire at 18 and 24 hours following discharge. Results reported no significant difference between groups at discharge and 18 hours following discharge. In contrast to the results reported by Higgins and colleagues (1994), none of the patients observed by Mixter and colleagues (1998) required narcotic supplemental analgesia, and all participants reported satisfactory pain control. This study demonstrated that combining preoperative KT with postoperative PO ibuprofen was safe and efficacious. It also suggests the benefit of using a long acting local anesthetic for pain control even when general anesthesia is used.

Ilkjær, Neilsen, Bach, Wernberg and Dahl (2000) aimed to see if an additive benefit on the pain control was gained by combining ibuprofen and the N-methyl-D-aspartate (NMDA) receptor antagonist dextromethorphan. They enrolled 100 women undergoing elective termination of pregnancy, considered a minimally invasive gynecological surgery. Previous research indicated that NMDA-receptors in the dorsal horn (spinal cord) mediated hyperexcitability following peripheral tissue insult (Dickenson, 1995). One hour prior to surgery, patients in the experimental groups received ibuprofen (400 mg orally), or dextromethorphan (120 mg orally), or a combination of both medications. The authors did not report the use of local anesthetic following induction of general anesthesia. Patients in the control group received a placebo medication one hour before surgery. Patients who received ibuprofen alone reported lower postoperative pain levels and less analgesic consumption than those who

received either dextromethorphan or the placebo. The combination of ibuprofen and dextromethorphan provided no added benefit. However, NMDA receptors are activated as central sensitization begins. The nociceptive summation during this minimally invasive procedure may have been insufficient to activate NMDA receptors and illustrate a benefit from dextromethorphan.

Many studies have evaluated the efficacy of preoperative analgesic medications to manage postoperative pain following third molar (wisdom teeth) surgery. Dionne and Cooper (1978) administered ibuprofen (400 mg) or a placebo to 90 participants 30 minutes prior to third molar surgery. Participants were instructed to take the postoperative analgesic (400 mg ibuprofen or 650 mg aspirin, equally distributed among both the experimental (pre-op ibuprofen) and control (pre-op placebo) groups) only when the pain became moderate or severe. However, the use of sedation and local anesthetic was not controlled. Some patients received sedation and local anesthesia while others only received local anesthesia. The experimental group receiving ibuprofen premedication used their postoperative medication 100 minutes later than the placebo group (control). In the experimental group, 17.7 percent reported severe pain initially, compared to 35.4 percent of participants in the control group reporting severe pain.

Pain outcomes from third molar extraction studies that have compared NSAIDS to other NSAIDS or opioids to NSAIDS may be misleading. Often investigators did not control the use general anesthesia, sedation and other analgesics that might confound results (Zaharias et al 1996, Joshi et al 2004). Zacharias, Hunter and Baker (1996) compared the effect of preoperative diclofenac (NSAID) to methadone in 40 participants, but reported that preoperative use of either NSAIDs or opiates may not be necessary if

patients receive adequate nerve blocks and intraoperative analgesics. The authors conceded that their study might have been underpowered to confidently detect a difference between placebo (n=12), diclofenac (n=13) and methadone (n=15). Furthermore, intra-operative analgesics, including tenoxicam (NSAID), dexamethasone (anti-inflammatory glucocorticoid) and postoperative paracetamol (opioid combination) may have obscured benefits afforded by pre-operative diclofenac and methadone.

Similarly, Joshi (2004) compared the effects of preoperative ibuprofen (600 mg), diclofenac (100 mg), paracetamol with codeine (1 g/60 mg), and placebo (Vitamin C 50 mg) among 119 participants who received general anesthesia for third molar surgery. No significant differences in postoperative pain levels were detected among groups. However, the placebo group reported significantly shorter ($p=0.009$) times before requesting postoperative analgesics (median 17 minutes; range 14 – 90 minutes). The diclofenac group had the longest median time to first request for analgesics (median 32 minutes; range 15-150 minutes) but this time was not significantly longer than the two analgesic groups. The authors suggested the anti-nociceptive treatment should be continued up to 12 to 24 hours postoperatively. They also recommended practitioners consider strategies other than a single pre-operative analgesic dose to manage postoperative pain, but they were not specific in their recommendation.

In 49 participants, Chiu and Cheung (2005) compared the efficacy of preoperative rofecoxib (COX2 inhibitor; 50 mg orally), or ibuprofen (400 mg) or placebo to positive control in a cross-over design. Patients had two separate surgeries. Unfortunately, how the anticipatory effect of receiving placebo at the first surgery might affect subsequent pain reports was not considered (Veerasarn and Stohler, 1992). The study demonstrates a

potential bias because patients who received placebo at the first surgery might be predisposed to report greater pain levels at the second surgery, and the results were grouped patients by medication category regardless of order. Reported pain scores were significantly lower in the rofecoxib group compared to placebo in the first six hours following surgery, and both rofecoxib and ibuprofen were superior to control.

Isiordia-Espinoza, Sanchez-Prieto, Tobias-Azua and Reyes-Garcia (2012) studied 30 patients receiving third surgery who were randomized to receive pre-operative either the NSAID meloxicam (15 mg IM) or tramadol (50 mg IM), a drug with central effects on serotonin, norepinephrine and μ -opioid receptors. Participants who received preoperative meloxicam reported significantly less postoperative pain and total analgesic consumption. This suggests the pain benefit of pharmacologically pre-operatively managing the peripheral traumatic inflammatory insult compared to using a central acting medication.

Periodontal Surgery

Trombelli Schincaglia, Zangari, Scapoli and Calura (1996) documented one of the few studies in the dental literature that evaluated the use of ketorolac tromethamine (KT 20 mg PO). Comparing pre-operative KT with placebo, the authors observed 48 participants following periodontal flap surgery. While reported pain levels at two to four hours following surgery were significantly lower, and the time to start taking the rescue drug (naproxen - NSAID) was significantly shorter for those who received KT (compared to placebo), the amount of rescue medication consumed by the two treatment groups was not significantly different.

Recent research from Brazil reported two studies of periodontal open flap debridement that evaluated preoperative use of two different NSAIDs and dexamethasone (Steffens, Santos & Pilatti, 2011a; Steffens, Santos, Sartori & Pilatti, 2011b). Study (2011a) with 56 participants evaluated for the efficacy of two selective COX2 inhibitors (celecoxib and etoricoxib) from one postoperatively up to the evening of the day after surgery and used placebo control. Participants were administered either a split dose (celcoxib 200mg preoperatively and 200mg 12 hours later) or a single dose (entoricoxib 120mg preoperatively). The entoricoxib group demonstrated significantly less rescue medication (750mg acetaminophen) ingestion than the placebo and celecoxib groups. No statistical difference in pain intensity existed between NSAID groups. Each allowed significantly lower pain intensity than the placebo group between two and seven hours postoperatively. There were no statistical differences observed between any of the groups on the second day between any of the groups. Authors thus concluded that a single preoperative dose of entoricoxib was no more effective than two split doses of celecoxib when used for pain prevention. The group's second study (2011b) also employed a placebo control and a crossover design as it evaluated the efficacy of etoricoxib (preoperatively 120mg) and dexamethasone (preoperatively 8mg) for pain prevention up to two days postoperatively. Dexamethasone and etoricoxib produced better pain control compared to the placebo group between four and eight hours postoperatively, and both intervention groups also consumed significantly less rescue medication compared to placebo. The authors concluded that a preemptive medication protocol of either etoricoxib or dexamethasone might be effective in reducing pain following open-flap debridement surgery.

The subjective pain management efficacy of NSAID and opioid combination medications is not well documented for periodontal surgery. Tucker, Smith and Adams (1996) compared the postoperative pain relief and adverse effects associated with a pretreatment regimen with etodolac (NSAID) to a typical *pro re nata* (PRN) regimen of combined acetaminophen and hydrocodone. In this single-blind study of 24 participants receiving osseous resective surgery 13 patients received etdolac and 11 had the combination acetaminophen and hydrocodone (dosage unspecified). The time span from preoperative dose to first postoperative dose was greater for patients who received etodolac. This suggested that preoperative NSAID provided longer initial postoperative comfort than afforded by a preoperative combination analgesic for patients using postoperative PRN analgesia.

Ketorolac Tromethamine to Manage Pain

Since Food and Drug Administration (FDA) approval in 1989, KT has been used to manage pain by many medical specialties using various routes of administration such as IV or IM. Chui and Gin (1995) compared the efficacy of preoperative dosing with diclofenac (75 mg IM) or KT (30 mg IM) on postoperative pain levels in a randomized controlled trial of 50 women receiving laparoscopic sterilization. If requested by the patient, a second dose of the study drug administered preoperatively as again administered in the recovery room followed by parenteral pethidine (opioid analgesic). No statistically significant differences in pain scores existed between the two groups at all time points. Four participants in the diclofenac group and five from the ketorolac group requested no further analgesies postoperatively. Over 71% of patients reported satisfactory analgesia after the second postoperative dose of the study analgesic (KT:

$15/20 = 75\%$; diclofenac: $15/21 = 71.4\%$). The authors concluded that both KT and diclofenac were effective in controlling pain following laparoscopic sterilization.

Mather and Peutrell (1995) observed the effects of preoperative administration paracetamol (PO), paracetamol (PO) plus IM KT, or IV morphine on postoperative analgesic consumption, nausea and vomiting in 80 randomized children (ages 3 to 12 years) receiving tonsillectomy. Paracetamol is acetaminophen. Eleven of eighty participants, even those who received preoperative morphine, required the rescue analgesic (IV morphine) in the recovery room. Those who received preoperative paracetamol plus IM KT required the least supplementary morphine. Postoperative nausea and vomiting were significantly reduced in the two groups that did not receive preoperative morphine. The authors concluded that most children's postoperative pain can be managed with a combination of IM KT and paracetamol, but a small number will require supplementary analgesia.

The relationship between levels of prostanoids from the site of tissue injury and analgesia was evaluated in 61 participants undergoing at least two partial bony or complete bony mandibular third molar extractions (Dionne, Gordon, Rowan, Kent & Brahimi, 2003). Prostanoids include prostaglandins (inflammatory mediators), thromboxanes (vasoconstriction mediators), and the prostacyclins (active in the resolution phase of inflammation.) Patients were assigned to three groups:

1. preoperative dexamethasone with IV KT at pain onset
2. preoperative dexamethasone with placebo at pain onset
3. preoperative placebo with placebo at pain onset.

Consistent with other microdialysis studies (Gordon, 2002; Khan, 2002; Roszkowski, 1997), patients who received KT suppressed both COX1 and COX2, demonstrated by a reduction in levels of both PGE2 (COX1 and COX2 product) and TXB2 (COX1 product) at the extraction sites. In the dexamethasone/placebo group TXB2 was significantly reduced, but PGE2 was not reduced to the same degree.

Turner and colleagues (2011) reported similar results among symptomatic endodontic patients who were given 12 mg IN KT preoperatively (30 minutes prior) and 12 mg IN KT postoperatively (immediately following procedure). Pain levels were assessed 15 and 30 minutes following initial dosage (before starting endodontic treatment), 30 minutes after completing treatment, and 4, 8, and 12 hours following the initial dose. Compared with placebo significantly better pain relief was achieved in the KT group at 30 minutes following the initial or second dose, and at 4 hours after the first IN dose ($p=0.03$).

Recent Advancements using Ketorolac

There are only three studies in the dental literature involving administration of KT through the nasal mucosa (Grant et al 2010, Turner et al 2011, Bockow et al 2013). Evaluating the absorption efficacy of KT by the sublingual mucosa has become a topic of interest as well (Trindale, Giglio, Colombini-Ishikirama, Calvo, Modena, Ribeiro, Dionisio, Brozoski, Lauris, Faria and Santos, 2012). A primary advantage of sublingual administration is increased rate of analgesic effect by avoiding the gastrointestinal route and avoiding first pass effect of the enterohepatic system, in which part of the available dose becomes metabolized. Another advantage is avoidance of the nasal mucosal and lacrimal discomfort associated with IN administration.

Trindale (2012) compared the clinical efficacy of sublingual KT and sublingual piroxicam (NSAID) in managing pain, trismus, and swelling in third molar extraction patients in a double blinded, randomized, crossover trial. Forty-seven participants randomly received either four days of sublingual KT (10 mg four times daily) or piroxicam (NSAID) sublingually (20 mg once daily) as the postoperative analgesic course after lower third molar extraction at two separate appointments. The outcome objectives evaluated included surgery duration, mouth opening, rescue analgesic medication, and facial swelling. In addition, patients documented postoperative pain and provided a global evaluation for seven days following surgery. There appeared to be no significant differences observed in any of the outcomes evaluated when comparing sublingual KT and piroxicam. In both groups, pain reports were low, use of rescue analgesic was low (paracetamol), mouth opening before and after surgery was similar, and there were no differences in the degree of facial swelling on the second or seventh days after surgery ($p>0.05$).

Several options to perform preoperative analgesic management exist. Well-controlled, experimental evidence demonstrates post-operative pain levels and rescue drug consumption are reduced in patients managed with pre-operative NSAIDs. Yet, few studies have evaluated the use of INKT as an adjunct to pain control in the dental setting. Following design of the clinical trial in concert with Roxro pharmaceuticals, Roxro was acquired and the new parent company discontinued active promotion of SPRIX® (INKT) and sponsorship of clinical trials. The randomized parallel-arm, placebo controlled clinical trial as described was therefore discontinued at the Walter Reed National Military Medical Center, Naval Postgraduate Dental School Periodontics Department.

Options to evaluate the postoperative effect of administering preoperative NSAID prior to periodontal surgery are worthy of further consideration and research. SPRIX® remains a novel means to effectively administer KT in an outpatient setting and may prove to be an effective adjunct to improve patient centered outcomes during and after periodontal surgery.

CHAPTER VI: CONCLUSIONS

Preoperative analgesic administration may minimize pain and postoperative analgesic consumption. However, dental research has yet to evaluate in highly painful procedures, such as quadrant periodontal flap surgery, the effect of preoperative administration of INKT on postoperative dental pain levels and post-operative analgesic consumption.

Appendix A:

Example of the pain diary to record sleep quality, pain levels and stress levels on a daily basis using the VAS scale

Study ID # _____	Surgery Date: _____
First Day after surgery	
Sleep Quality	
0	10
No sleep	Best Sleep Imaginable
Pain levels	
Upon waking	
0	10
No Pain	Worst Pain Imaginable
Midday before lunch	
0	10
No Pain	Worst Pain Imaginable
Before bed	
0	10
No Pain	Worst Pain Imaginable
Stress at end of day	
0	10
No stress	Worst Stress

REFERENCES

Allen SC, Ravindran D. Perioperative use of nonsteroidal anti-inflammatory drugs: results of a UK regional audit. *Clin Drug Investig.* 2009;29(11):703-11.

Bacon R, Newman S, Rankin L, Pitcairn G, Whiting R. Pulmonary and nasal deposition of ketorolac tromethamine solution (SPRIX) following intranasal administration. *International Journal of Pharmacology* 2012;431(1-2): 39-44.

Bailey B, McManus BC. Treatment of children with migraine in the emergency department: a qualitative systematic review. *Pediatr Emerg Care* 2008; 24(5): 321-30.

Beilin B, Shavit Y, Trabekin E, Mordashev B, Mayburd E, Zeidel A, Bessler H. The effects of postoperative pain management on immune response to surgery. *Anesthesia and Analgesia* 2003;97(3): 822- 827.

Ben-David B, Baune-Goldstein U, Goldik Z, Gaitini L. Is preoperative ketorolac a useful adjunct to regional anesthesia for inguinal herniorrhaphy? *Acta Anaesthesiologica Scandinavica* 1996;40(3):358-363.

Besedovsky HO, Del Rey A. Immune-neuro-endocrine interactions: Facts and hypotheses. *Endocrine Reviews* 1996;17(1): 64–102.

Bockow R, Korostoff J, Pinto A, Hutcheson M, Secrcto SA, Bodner L, Hersh EV. Characterization and treatment of postsurgical dental implant pain employing intranasal ketorolac. *Compend Contin Educ Dent* 2013; 34(8): 570-576.

Boyer KC, McDonald P, Zoetis T. A novel formulation of ketorolac tromethamine for intranasal administration: preclinical safety evaluation. *International Journal of Toxicology* 2010; 29(5): 467-478.

Braaten KP, Hurwitz S, Fortin J, Goldberg AB. Intramuscular ketorolac versus oral ibuprofen for relief in first-trimester surgical abortion: a randomized clinical trial. *Contraception* 2014; 89(2): 116-21.

Brown C, Moodie J, Bisley E, Bynum L. Intranasal ketorolac for postoperative pain: a phase 3, double-blind, randomized study. *Pain Medicine* 2009;10(6): 1106-1114. Epub 2009 Jul 6. Erratum in: *Pain Medicine* 2011;12(6): 990. Dosage error in published abstract; MEDLINE/PubMed abstract corrected.

Buckenmaier, CC 3rd. The role of pain management in recovery following trauma and orthopaedic surgery. *The Journal of the American Academy of Orthopaedic Surgeons* 2012; 20 Suppl 1: S35-S38.

Budd K. Pain management: Is opioid immunosuppression a clinical problem? *Biomedicine & Pharmacotherapy* 2006;60(7):310- 317

Chang JE, Chin W, Simon R. Aspirin-sensitive asthma and upper airway diseases.

American Journal of Rhinology and Allergy 2012;26(1): 27-30.

Chelladurai S, Mishra M, Mishra B. Design and evaluation of bioadhesive in-situ nasal gel of ketorolac tromethamine. *Chemical & Pharmaceutical Bulletin (Tokyo)*.

2008;56(11): 1596-1599.

Chiou WK, Cheung LK. Efficacy of preoperative oral rofecoxib in pain control for third molar surgery. *Oral Surgery Oral Medicine Oral Pathology Oral Radiology Endodontics* 2005; 99(6): e47-53.

Chui PT, Gin T. A comparison between ketorolac and diclofenac in laparoscopic sterilization. *European Journal of Anaesthesiology* 1995;12(6): 597-601.

Curtis JW, McLain JB. The incidence and severity of complications and pain following periodontal surgery. *Journal of Periodontology* 1985; 56(10): 597-601.

DeLeo JA, Yezierski RP. The role of neuroinflammation and neuroimmune activation in persistent pain. *Pain* 2001;90(1): 1– 6.

Dickenson AH. The spinal pharmacology of pain. *Br J Anaesth* 1995; 75: 193-200.

Dionne RA, Cooper SA. Evaluation of preoperative ibuprofen for postoperative pain after removal of third molars. *Oral Surgery Oral Medicine Oral Pathology* 1978; 45(6): 851-856.

Dionne RA, Gordon SM, Rowan J, Kent A, Brahim JS. Dexamethasone Suppresses Peripheral Prostanoid Levels Without Analgesia in a Clinical Model of Acute Inflammation. *Journal of Oral and Maxillofacial Surgery* 2003; 61(9):997-1003.

Drover DR, Hammer GB, Anderson BJ. The pharmacokinetics of ketorolac after single postoperative intranasal administration in adolescent patients. *Anesthesia & Analgesia*. 2012;114(6): 1270-1276.

Farrar JT, Portenoy RK, Berlin JA, Kinnan JL, Strom BL. Defining the clinically important difference in pain outcome measures. *Pain* 2000; 88(3):287-294.

FDA Website 2005, COX 2 inhibitor adverse outcomes
[http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandP
roviders/ucm103420.htm#COX2](http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103420.htm#COX2)

Garnock-Jones KP. Intranasal ketorolac: for short-term pain management. *Clinical Drug Investigation* 2012 Jun 1;32(6): 361-71.

Goodsell DS. The molecular perspective: Morphine. *Stem Cells* 2005;23(1): 144- 145.

Gordon SM, Brahim JS, Rowan J, Kent A, Dionne RA. Peripheral prostanoïd levels and NSAID analgesia: Replicate clinical trials in a tissue injury model. *Clinical Pharmacology and Therapeutics* 2002; 72(2): 175-183.

Grant GM, Mehlisch DR. Intranasal ketorolac for pain secondary to third molar impaction surgery: a randomized, double-blind, placebo-controlled trial. *Journal of Oral Maxillofac Surgery* 2010;68(5): 1025-1031. Epub 2010 Mar 5.

Griffin TJ, Cheung WS, Zavras AI, Damoulis PD. Postoperative complications following gingival augmentation procedures. *Journal of Periodontology* 2006; 77(12): 2070-2079.

Higgins MS, Givogre JL, Marco AP, Blumenthal PD, Furman WR. Recovery from outpatient laparoscopic tubal ligation is not improved by preoperative administration of ketorolac or ibuprofen. *Anesthesia and analgesia* 1994; 79(2): 274-280.

Ilkjær S, Neilsen PA, Bach LF, Wernberg M, Dahl JB. The effect of dextromethorphan, alone or in combination with ibuprofen, on postoperative pain after minor gynaecological surgery. *Acta Anaesthesiologica Scandinavica* 2000 44(7): 873-877.

Intranasal ketorolac (Sprix). *The Medical Letter on Drugs and Therapeutics* 2012 Jan 23;54(1382):7-8.

Isiordia-Espinoza MA, Sanchez-Prieto M, Tobias-Azuq F, Reyes-Garcia JG. Pre-emptive analgesic effectiveness of Meloxicam versus Tramadol after mandibular third molar surgery: A pilot study. *Journal of Oral and Maxillofacial Surgery* 2012; 70(1): 31-36.

Jackson DL, Moore PA, Hargreaves KM. Preoperative nonsteroidal anti-inflammatory medication for the prevention of postoperative dental pain. *Journal of the American Dental Association* 1989; 119(5): 641-647.

Joshi A, Parara E, Mafarlane TV. A double-blind randomised controlled clinical trial of the effect of preoperative ibuprofen, diclofenac, paracetamol with codeine and placebo tablets for relief of postoperative pain after removal of impacted third molars. *British Journal of Oral and Maxillofacial Surgery* 2004; 42(4): 299-306.

Joshi GP, Ogunnaike BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. *Anesthesiology Clinics of North America* 2005; 23(1): 21-36.

Khan AA, Brahim JS, Rowan JS, Dionne RA. In vivo selectivity of a selective cyclooxygenase-2 inhibitor in the oral surgery model. *Clinical Pharmacology and Therapeutics* 2002; 72(1): 44-49.

Kim K, Brar P, Jakubowski J, Kaltman S, Lopez E. The use of corticosteroid and nonsteroidal anti-inflammatory medication for the management of pain and inflammation

after third molar surgery: A review of the literature. *Oral Surgery Oral Medicine Oral Pathology Oral Radiology Endodontics* 2009; 107(5): 630-640.

Lee RU, White AA, Ding D, Dursun AB, Woessner KM, Simon RA, Stevenson DD. Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin-exacerbated respiratory disease. *Annals of Allergy, Asthma & Immunology* 2010;105(2): 130-135.

Maroli S, Srinath HP, Goinka C, Yadav NS, Bhardwaj A, Varghese RK. Sniffing out pain: An in vivo intranasal study of analgesic efficacy. *J Int Oral Health* 2014; 6(1): 66-71.

Mather SJ, Peutrell JM. Postoperative morphine requirements, nausea and vomiting following anaesthesia for tonsillectomy. Comparison of intravenous morphine and non-opioid analgesic techniques. *Paediatric Anaesthesia* 1995;5(3): 185-188.

Matoulková P, Dosedel M, Růžková B, Kubena A. Information and awareness concerning ibuprofen as an ingredient in over the counter analgesics: a questionnaire-based survey of residents of retirement communities. *Acta Pol Pharm.* 2013 Mar-Apr; 70(2):333-8.

McAleer SD, Majid O, Vcnables E, Polack T, Sheikh MS. Pharmacokinetics and safety of ketorolac following single intranasal and intramuscular administration in healthy volunteers. *Journal of Clinical Pharmacology* 2007;47(1): 13-18.

McCaffery M, Pasero C. *Pain: Clinical Manual*, St. Louis, 1999, P. 16. (Mosby) *Pain Management: Theory and Practice*, edited by RK Portenoy & RM Tanner, copyright 1996 by Oxford University Press, Inc.

Mickel AK, Wright AP, Chogle S, Jones JJ, Kantorovich I, Curd F. An analysis of current analgesic preferences for endodontic pain management. *J Endod*. 2006 Dec;32(12):1146-54. Epub 2006 Oct 19..

Mixer CG 3rd, Meeker LD, Gavin TJ. Preemptive pain control in patients having laparoscopic hernia repair: a comparison of ketorolac and ibuprofen. *Archives of Surgery* 1998; 133(4): 432-437.

Moodie JE, Brown CR, Bisley EJ, Weber HU, Bynum L. The safety and analgesic efficacy of intranasal ketorolac in patients with postoperative pain. *Anesthesia and Analgesia*. 2008 Dec;107(6): 2025-2031. Erratum in: *Anesthesia and Analgesia*. 2009;108(3): 991. Dosage error in published abstract; MEDLINE/PubMed abstract corrected; Dosage error in article text.

Nagda CD, Chotai NP, Nagda DC, Patel SB, Patel UL. Development and characterization of mucoadhesive microspheres for nasal delivery of ketorolac. *Pharmazie* 2011;66(4): 249-257.

Paech MJ, Lim CB, Banks SL, Rucklidge MWM, Doherty DA. A new formulation of nasal fentanyl spray for postoperative analgesia: a pilot study. *Anaesthesia* 2003; 58(8): 740-744.

Pfaffenrath V, Fenzl E, Bregman D, Färkkila M. Intranasal ketorolac tromethamine (SPRIX(R)) containing 6% of lidocaine (ROX-828) for acute treatment of migraine: Safety and efficacy data from a phase II clinical trial. *Cephalgia* 2012 Jul;32(10): 766-77. Epub 2012 Jun 18.

Pickering AE, Bridge HS, Nolan J, Stoddart PA. Double-blind, placebo-controlled analgesic study of ibuprofen or rofecoxib in combination with paracetamol for tonsillectomy in children. *British Journal Anaesthesia* 2002;88(1): 72-77.

Quadir M, Zia H, Needham TE. Development and evaluation of nasal formulations of ketorolac. *Journal of Drug Delivery* 2000;7(4): 223-229.

Rashwan WA. The efficacy of acetaminophen-caffeine compared to Ibuprofen in the control of postoperative pain after periodontal surgery: a crossover pilot study. *Journal of Periodontology* 2009;80(6): 945-952.

Rainsford KD. Discovery, mechanisms of action and safety of ibuprofen. *Int J Clin Pract Suppl.* 2003; 135:3-8.

Roszkowski MT, Swift JQ, Hargreaves KM. Effect of NSAID administration on tissue levels of immunoreactive PGE2, leuko- triene B4 and (S)-flurbiprofen following extraction of impacted third molars. *Pain* 1997 73(3): 339-345.

Rubin P, Yee JP, Ruoff G. Comparison of long-term safety of ketorolac trometamine and aspirin in the treatment of chronic pain. *Pharmacotherapy* 1990; 10(6): 106S-110S.

Sabatowski R, Schäfer D, Kasper SM, Brunsch H, Radbruch L. Pain treatment: A historical overview. *Current Pharmaceutical Design* 2004;10(7): 701-716.

Sacerdote P. Opioids and the immune system. *Palliative Medicine* 2006;20(Suppl 1): S9-S15.

Safieh-Garabedian B, Poole S, Allchorne A, Winter J, Woolf CJ. Contribution of interleukin-1 beta to the inflammation-induced increase in nerve growth factor levels and inflammatory hyperalgesia. *Br J Pharmacol* 1995; 115(7): 1265-75.

Sankar C, Mishra B. Development and in vitro evaluations of gelatin A microspheres of ketorolac tromethamine for intranasal administration. *Acta Pharmaceutica* 2003 Jun;53(2): 101-110.

Santus G, Rivolta R, Bottoni G, Testa B, Canali S, Peano S. Nasal formulations of ketorolac tromethamine: technological evaluation—bioavailability and tolerability in rabbits. *Farmaco* 1993;48(12): 1709-1723.

Sarkar C, Das B, Baral P. An audit of drug prescribing practices of dentists. *Indian J Dent Res.* 2004 Apr-Jun;15(2):58-61.

Singla N, Singla S, Minkowitz HS, Moodie J, Brown C. Intranasal ketorolac for acute postoperative pain. *Current Medical Research and Opinion* 2010 Aug;26(8):1915-1923.
Erratum in: *Current Medical Research and Opinion* 2012 Jun;28(6):1052.

Snyder MB, Bregmen DB. SPRIX (ketorolac tromethamine) nasal spray: a novel nonopioid alternative for managing moderate to moderately severe dental pain. *Compendium of Continuing Education in Dentistry* 2012;33 Spec No 1(1): 2-11.

Steffens JP, Santos FA, Pilatti GL. The use of etoricoxib and celecoxib for pain prevention after periodontal surgery: a double-masked, parallel-group, placebo-controlled, randomized clinical trial. *Journal of Periodontology* 2011;82(9): 1238-44.

Steffens JP, Santos FA, Sartori R, Pilatti GL. Preemptive dexamethasone and etoricoxib for pain and discomfort prevention after periodontal surgery: a double-masked, crossover, controlled clinical trial. *Journal of Periodontology* 2011;81(8): 1153-1160.

Subaiea GM, Alansi BH, Serra DA, Alwan M, Zawia NH. The ability of tolfenamic acid to penetrate the brain: a model for testing the brain disposition of candidate Alzheimer's drugs using multiple platforms. *Curr Alzheimer Res.* 2011 Dec;8(8):860-7.

Sweitzer SM, Colburn RW, Rutkovski M, DeLeo JA. Acute peripheral inflammation induces moderate glial activation and spinal IL-1 β expression that correlates with pain behavior in the rat. *Brain Research* 1999;829(1-2): 209–221.

Trindade PAK, Giglio FPM, Colombini-Ishikirama BL, Calvo AM, Modena KCS, Ribeiro DA, Dionisio TJ, Brozoski DT, Lauris JRP, Faria FAC, Santos CF. Sublingual ketorolac and sublingual piroxicam are equally effective for postoperative pain, trismus, and swelling management in lower third molar removal. *Oral Surgery Oral Medicine Oral Pathology Oral Radiology* 2012; 114(1): 27-34.

Trombelli L, Schincaglia GP, Zangari F, Scapoli C, Calura G. Effect of pretreatment with ketorolac tromethamine on post-operative pain following periodontal surgery. *Journal of Clinical Periodontology* 1996; 23(2): 128-132

Tucker PW, Smith JR, Adams DF. A comparison of 2 analgesic regimens for the control of postoperative periodontal discomfort. *Journal of Periodontology* 1996;67(2): 125-129.

Turk DC, Okifuji A (2010). Pain terms and taxonomies of pain. In Fishman, SM, Ballantyne JC, Rathmell JP, *Bonica's Management of Pain* (Fourth Ed., 13-23). Philadelphia, PA: Lippincott Williams & Wilkins.

Turner CL, Eggleston GW, Lunos S, Johnson N, Wiedmann TS, Bowles WR. Sniffing out endodontic pain: use of an intranasal analgesic in a randomized clinical trial. *Journal of Endodontics* 2011;37(4): 439-444.

Vane JR, Bakhle YS, Botting RM. Cyclooxygenases 1 and 2. *Annual Review of Pharmacology and Toxicology*. 1998;38: 97-120.

Veersasarn P and Stohler CS. The effect of experimental muscle pain on the background electrical brain activity. *Pain*. 1992;49:349-360.

Wessel JR, Tatakis DN. Patient outcomes following subepithelial connective tissue graft and free gingival graft procedures. *Journal of Periodontology* 2008; 79(3): 425-430.

White A, Bigby T, Stevenson D. Intranasal ketorolac challenge for the diagnosis of aspirin-exacerbated respiratory disease. *Annals of Allergy, Asthma & Immunology* 2006;97(2): 190-195.

Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs* 2005; 14(7): 798-804.

Woolf CJ, American College of Physicians, American Physiological Society. Pain: Moving from symptom control toward mechanism-specific pharmacologic management. *Annals of Internal Medicine* 2004;140(6): 441-451.

Wright JM, Price SD, Watson WA. NSAID use and efficacy in the emergency department: single doses of oral ibuprofen versus intramuscular ketorolac. *Ann Pharmacother* 1994; 28(3):309-12.

Xu JJ, Sowerby L, Rotenberg BW. Aspirin desensitization for aspirin-exacerbated respiratory disease (Samter's Triad): a systematic review of the literature. *Int Forum Allergy Rhinol* 2013 3(11): 915-920.

Zacharias M, Hunter KM, Baker B. Effectiveness of Preoperative Analgesics on Postoperative Dental Pain: A Study. *Anesthesia Progress* 1996; 43:92-96.